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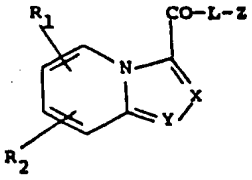
(54) **Azabicyclic compounds, process for their preparation, and their pharmaceutical use.**

(57) Compounds of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

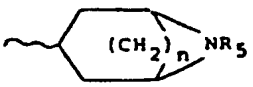
L is NH or O;

X is N or CR_3 wherein R_3 is hydrogen or C_{1-6} alkoxy;

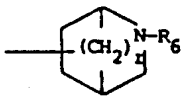
Y is N or CR_4 wherein R_4 is hydrogen, halogen, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulphonyl, C_{1-6} alkylsulphinyl, C_{1-7} acyl, cyano, C_{1-6} alkoxycarbonyl, C_{1-7} acylamino, hydroxy, nitro or amino, aminocarbonyl, or aminosulphonyl, optionally N-substituted by one or two groups selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{3-6} cycloalkyl C_{1-4} alkyl or disubstituted by C_4 or C_5 polymethylene; phenyl or phenyl C_{1-4} alkyl group optionally substituted in the phenyl ring by one or two of halogen, C_{1-6} alkoxy or C_{1-6} alkyl groups.

R_1 and R_2 are independently selected from hydrogen, or halogen;

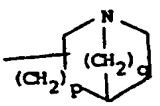
Z is a group of formula (a), (b) or (c):



(a)



(b)



(c)

wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3; and

R_5 or R_6 is C_{1-4} alkyl; having 5-HT$_3$ antagonist activity, a process for their preparation and their use as pharmaceuticals.

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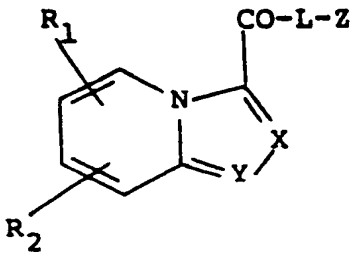
NOVEL COMPOUNDS

This invention relates to novel compounds having useful pharmacological properties, to pharmaceutical compositions containing them, to a process and intermediates for their preparation, and to their use as pharmaceuticals.

GB 2100259A and 2125398A, and EP-A-158265 describe esters and amides having an azabicyclic side chain and possessing 5-HT_3 antagonist activity.

A class of novel, structurally distinct compounds has now been discovered. These compounds have 5-HT_3 antagonist activity.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

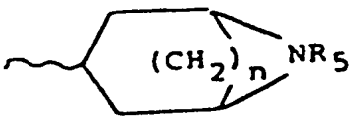
wherein

L is NH or O;

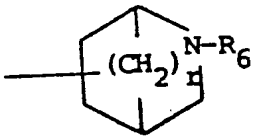
X is N or CR_3 wherein R_3 is hydrogen or C_{1-6} alkoxy;
Y is N or CR_4 wherein R_4 is hydrogen, halogen, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulphonyl, C_{1-6} alkylsulphinyl, C_{1-7} acyl, cyano, C_{1-6} alkoxycarbonyl, C_{1-7} acylamino, hydroxy, nitro or amino, aminocarbonyl, or aminosulphonyl, optionally N-substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, and C_{3-8} cycloalkyl C_{1-4} alkyl or disubstituted by C_4 or C_5 polymethylene; phenyl or phenyl C_{1-4} alkyl group optionally substituted in the phenyl ring by one or two of halogen, C_{1-6} alkoxy or C_{1-6} alkyl groups.

R_1 and R_2 are independently selected from hydrogen, or halogen;

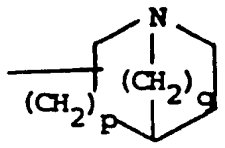
Z is a group of formula (a), (b) or (c):



(a)



(b)



(c)

wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3; and

R_5 or R_6 is C_{1-4} alkyl.

Often L is NH.

Suitable values for X include N, or CR_3^1 wherein R_3^1 is hydrogen, methoxy, ethoxy, n- or iso-propoxy. Often X is N, CH or COMe.

Suitable values for Y include N, or CR_4^1 wherein R_4^1 is hydrogen, fluoro, chloro, bromo, CF_3, methyl, ethyl, methoxy, ethoxy, methylthio, ethylthio, methylsulphonyl, ethylsulphonyl, methylsulphinyl, ethylsulphinyl, acetyl, propionyl, cyano, methoxycarbonyl, ethoxycarbonyl, acetylamino, hydroxy, nitro; and amino, aminocarbonyl, or aminosulphonyl, any of which may be optionally substituted by one or two methyl groups or by a cyclopentyl or cyclohexyl group or R_4^1 is phenyl or benzyl optionally substituted by one or two methyl, methoxy, bromo, chloro or fluoro groups. Often Y is N, CH or CCH_3, preferably CCH_3.

Values for R_1 and/or R_2 include hydrogen, fluoro, chloro or bromo. Preferably R_1 and R_2 are both hydrogen.

Preferably n is 2 or 3 and p, q and r are 1 or 2.

Examples of R_5/R_6 include as groups of interest C_{1-3} alkyl such as methyl, ethyl and n- and iso-propyl. R_5/R_6 is preferably methyl or ethyl, most preferably methyl.

There is a group of compounds within formula (I) wherein R_4 is hydrogen or C_{1-6} alkyl and the remaining variables are as defined in formula (I).

The pharmaceutically acceptable salts of the compounds of the formula (I) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α-keto glutaric, α-glycerophosphoric, and glucose-1-phosphoric acids.

The pharmaceutically acceptable salts of the compounds of the formula (I) are usually acid addition salts with acids such as hydrochloric, hydrobromic, phosphoric, sulphuric, citric, tartaric, lactic and acetic acid.

Preferably the acid addition salt is the hydrochloride salt.

Examples of pharmaceutically acceptable salts include quaternary derivatives of the compounds of formula (I) such as the compounds quaternised by compounds R_a-T wherein R_a is C_{1-6} alkyl, phenyl-C_{1-6} alkyl or C_{5-7} cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of R_a include methyl, ethyl and n- and iso-propyl; and benzyl and phenethyl. Suitable examples of T include halide such

as chloride, bromide and iodide.

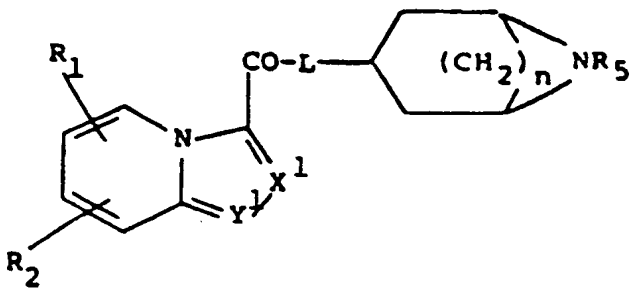
Examples of pharmaceutically acceptable salts also include internal salts such as N-oxides.

The compounds of the formula (I), their pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included wherever a compound of formula (I) or a salt thereof is herein referred to.

It will of course be realised that some of the compounds of the formula (I) have chiral or procniral centres and thus are capable of existing in a number of stereoisomeric forms including enantiomers. The invention extends to each of these stereoisomeric forms (including enantiomers), and to mixtures thereof (including racemates). The different stereoisomeric forms may be separated one from the other by the usual methods.

It will also be realised that compounds of formula (I) may adopt an endo or exo configuration with respect to L. The endo configuration is preferred.

A group of compounds within formula (I) is of formula (II):

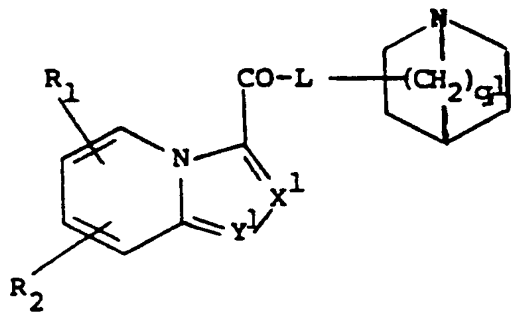


(II)

wherein X^1 is N, H or $COCH_3$, Y^1 is N, H or C-$R_4{}^1$ as defined and the remaining variables are as defined in formula (I).

Examples of the variables and preferred variables are as so described for corresponding variables in relation to formula (I).

A further group of compounds within formula (I) is of formula (III):

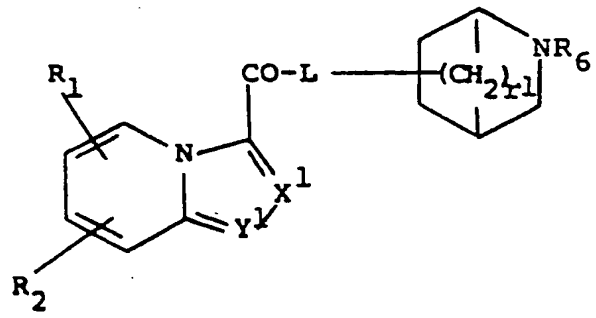


(III)

wherein q^1 is 1 or 2 and the remaining variables are as defined in formulae (I) and (II).

Examples of the variables and preferred variables are as so described for the corresponding variables in formula (I).

There is a further group of compounds within formula (I) of formula (IV):

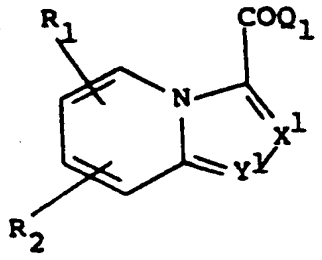


(IV)

wherein r^1 is 1 or 2 and the remaining variables are as defined in formulae (I) and (II).

Examples of the variables and preferred variables are so described as the corresponding variables in formula (I).

The invention also provides a process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (V):



(V)

with a compound of formula (VI):

$$H - L - Z^1 \qquad (VI)$$

or a reactive derivative thereof, when L is O;

wherein Q_1 is a leaving group; Z^1 is Z as defined or wherein R_5/R_6 is replaced by a hydrogenolysable protecting group; and the remaining variables are as hereinbefore defined; and thereafter optionally converting any R_1 and/or R_2 group to another R_1/R_2 group respectively, converting Z^1, when other than Z,

to Z; and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

Examples of leaving groups Q_1, displaceable by a nucleophile, include halogen such as chloro and bromo, C_{1-4} alkoxy, such as CH_3O and C_2H_5O-, PhO-, or activated hydrocarbyloxy, such as Cl_5C_6O- or Cl_3CO-

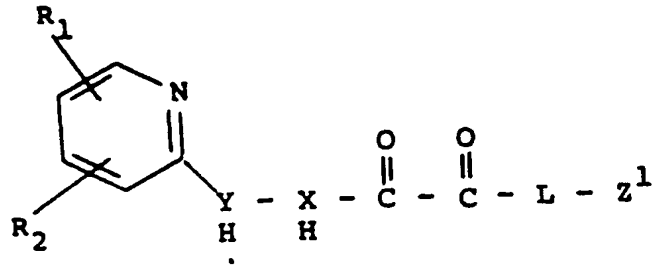
If a group Q_1 is a halide, then the reaction is preferably carried out at non-extreme temperatures in an inert non-hydroxylic solvent, such as benzene, dichloromethane, toluene, diethyl ether, tetrahydrofuran (THF) or dimethylformamide (DMF). It is also preferably carried out in the presence of an acid acceptor, such as an organic base, in particular a tertiary amine, such as triethylamine, trimethylamine, pyridine or picoline, some of which can also function as the solvent. Alternatively, the acid acceptor can be inorganic, such as calcium carbonate, sodium carbonate or potassium carbonate. Temperatures of 0^o-100^oC, in particular 10-80^oC are suitable.

If a group Q_1 is C_{1-4} alkoxy, phenoxy or activated hydrocarbyloxy then the reaction is preferably carried out in an inert polar solvent, such as tolene or dimethylformamide. It is also preferred that the group Q_1 is Cl_3CO- and that the reaction is carried out in toluene at reflux temperature.

When L is O the compound of formula (VI) may be in the form of a reactive derivative thereof, which is often a salt, such as the sodium or potassium salt.

The invention provides a further process for the preparation of a compound of formula (I) wherein X is

N, or a pharmaceutically acceptable salt thereof, which process comprising cyclising a compound of formula (VIII):

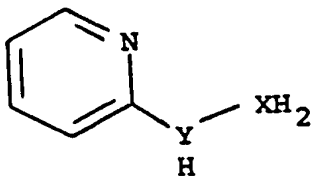


(VII)

wherein the variables are as hereinbefore defined; and thereafter optionally converting any R_1 and/or R_2 group to another R_1/R_2 group respectively, converting Z^1 when other than Z, to Z; and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

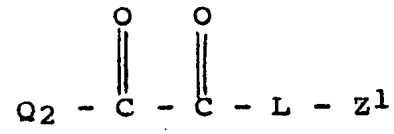
The cyclisation reaction may be effected by heating in an inert solvent, such as xylene or decalin or heating with a dehydrating agent, such as phosphorus oxychloride.

A compound of formula (VII) may be prepared by the reaction of a compound of formula (VIII):



(VIII)

with a compound of formula (IX):



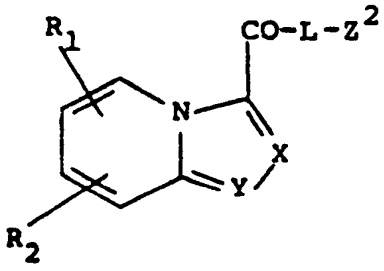
(IX):

wherein Q_2 is a leaving group and the remaining variables are as hereinbefore defined.

Q_2 is a leaving group as hereinbefore defined for Q_1 and the reaction is carried out in accordance with the conditions described herein for the reaction between the compounds of formulae (V) and (VI), wherein L is NH.

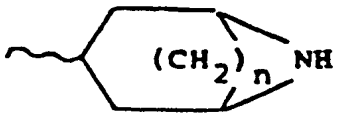
It will be apparent that compounds of the formula (I) containing an R_1 or R_2 group which is convertible to another R_1 or R_2 group are useful novel intermediates. i.e. a hydrogen substituent is convertible to a halogen substituent by halogenation using conventional halogenating agents.

Z^1 when other than Z may have a hydrogenolysable protecting group which is benzyl optionally substituted by one or two groups as defined for R_1 and R_2. Such benzyl groups may, for example, be removed, when R_1 or R_2 is not halogen, by conventional transition metal catalysed hydrogenolysis to give compounds of the formula (X):

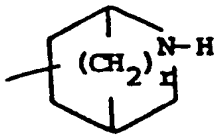


(X)

wherein Z^2 is of formula (d) or (e):



(d)



(e)

wherein the variables are as defined in formula (I).

This invention also provides a further process for the preparation of a compound of the formula (I) which comprises N-alkylating a compound of formula (X), and optionally forming a pharmaceutically acceptable salt, of the resulting compound of the formula (I).

In this further process of the invention 'N-alkylation' comprises the substitution of the N-atom depicted in formula (X) by any group R_5/R_6 as hereinbefore defined. This may be achieved by reaction of the compound of formula (X) with a compound R_5Q_3 or R_6Q_3

wherein R_5 and R_6 are as hereinbefore defined and Q_3 is a leaving group.

Suitable values for Q_3 include groups displaced by nucleophiles such as Cl, Br, I, OSO_2CH_3 or $OSO_2C_6H_4pCH_3$.

Favoured values for Q_3 include Cl, Br and I.

The reaction may be carried out under conventional alkylation conditions for example in an inert solvent such as dimethylformamide in the presence of an acid acceptor such as potassium carbonate. Generally the reaction is carried out at non-extreme temperature such as at ambient or slight above.

Alternatively, 'N-alkylation' may be effected under conventional reductive alkylation conditions when the group R_5 or R_6 in the compound of formula (I) contains a methylene group adjacent to the N-atom in the bicycle.

Interconverting R_5 or R_6 in the compound of the formula (X) before coupling with the compound of the formula (V) is also possible. Such interconversions are effected conveniently under the above conditions. It is desirable to protect any amine function witn a group readily removable by acidolysis such as a C_{2-7} alkanoyl group, before R_5/R_6 interconversion.

When R_5 or R_6 in the compound of formula (VI) contains a methylene group adjacent to the N-atom in the bicycle it is often convenient in the preparation of such a compound of formula (VI) to prepare the corresponding compound wherein the methylene group is replaced by -CO-, or for R_5 or R_6 is methyl, where the methyl group

is replaced by alkoxycarbonyl. Such compounds may then be reduced using a strong reductant such as lithium aluminium hydride to the corresponding compound of formula (V).

The compounds of formula (V), (VI), (VIII) and (IX) are known or are preparable analogously to, or routinely from, known compounds.

Compounds of the formula (VI) wherein Z is of formula (c) may be prepared as described in European Patent Publication No. 115933 or by analogous methods thereto. Compounds of the formulae (VII) and (X) are novel and form an aspect of the invention.

It will be realised that in the compound of the formula (I) the -CO-L- linkage may have an endo or exo orientation with respect to the ring of the bicyclic moiety to which it is attached. A mixture of endo and exo isomers of the compound of the formula (I) may be synthesised non-stereospecifically and the desired isomer separated conventionally therefrom e.g. by chromatography; or alternatively the endo and exo isomer may if desired by synthesised from the corresponding endo or exo form of the compound of the formula (VI).

Pharmaceutically acceptable salts of the compounds of this invention may be formed conventionally.

The salts may be formed for example by reaction of the base compound of formula (I) with a pharmaceutically acceptable organic or inorganic acid.

The compounds of the present invention are 5-HT antagonists and it is thus believed may generally be

used in the treatment or prophylaxis of migraine, cluster headaches and trigeminal neuralgia; and also as anti-emetics, in particular that of preventing vomiting and nausea associated with cancer therapy, and motion sickness. Examples of such cancer therapy include that using cytotoxic agents, such as cisplatin, doxorubicin and cyclophosphamide, particularly cisplatin; and also radiation treatment. Compounds which are 5-HT antagonists may also be of potential use in the treatment of CNS disorders such as anxiety and psychosis; arrhythmia, obesity and gastrointestinal disorders such as irritable bowel syndrome.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art, for example with an enteric coating.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

The oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

The invention further provides a method of treatment or prophylaxis of migraine, cluster headache, trigeminal neuralgia and/or emesis in mammals, such as humans, which comprises the administration of an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

An amount effective to treat the disorders hereinbefore described depends on the relative efficacies of the compounds of the invention, the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70kg adult will normally contain 0.5 to 1000mg for example 1 to 500mg, of the compound of the invention. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of approximately 0.001 to 50mg/kg/day, more usually 0.002 to 25 mg/kg/day.

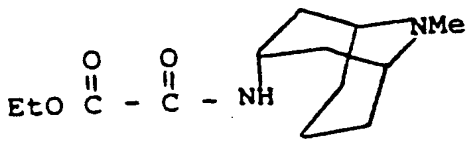
No adverse toxicological effects are indicated at any of the aforementioned dosage ranges.

The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for use in the treatment of migraine, cluster headache, trigeminal neuralgia and/or emesis.

The following Examples illustrate the preparation of compounds of formula (I); the following descriptions illustrate the preparation of intermediates.

Description 1

(endo)-N-(9-Methyl-9-azabicyclo[3,3,1]non-3-yl) ethyl oxamate (D1)



(D1)

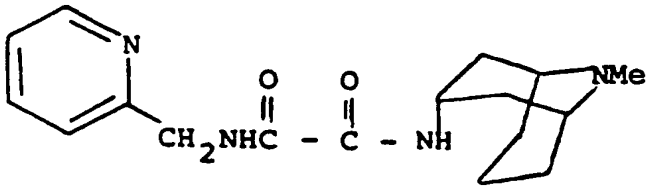
To a stirred solution of (endo)-9-metnyl-9-azabicyclo-[3,3,1]-nonan-3-amine (5.0g) and triethylamine (5ml) in CH_2Cl_2 (200ml) at 0°C was added, dropwise, a solution of ethyl oxalyl chloride (4.0ml) in CH_2Cl_2 (10ml). After 1h, the reaction mixture was washed with saturated $NaHCO_3$ solution (100ml), dried (K_2CO_3) and concentrated in vacuo. Trituration of the residue with ether afforded the title compound (D.1) (5.3g).

m.p. 105-9°C

^1H-nmr($CDCl_3$)δ	7.0	-6.5	(m, 1H)
	4.2		(q superimposed on m, 3H)
	3.2	-2.8	(m, 2H)
	2.6	-0.8	(m, 16H including 2.40, s, 3H and 1.35, t, 3H).

Description 2

(endo)-N-(9-Methyl-9-azabicyclo[3,3,1]non-3-yl)-N'-(2-pyridyl-methyl)oxamide (D.2)



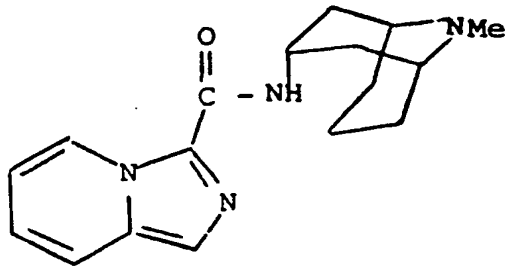
(D2)

A solution of 2-aminomethyl pyridine (0.42g) and (endo)-N-(9-methyl-9-azabicyclo[3,3,1]non-3-yl) ethyl oxamate (D.1) (1.0g) in xylene (10ml) were heated under reflux until the reaction was complete by T.L.C. The solvent was removed in vacuo and the residue triturated with ether/petrol to give the title compound (D.2) (0.63g).

^{1}H-nmr($CDCl_3$)δ 8.7 -8.2 (m, 2H)
7.7 -6.8 (m, 4H)
4.5 (d, 2H)
4.6 -3.8 (m, 1H)
3.2 -2.7 (m, 2H)
2.65-0.8 (m, 13H including 2.40, s, 3H)

Example 1

(endo)-N-(9-Methyl-9-azabicyclo[3.3.1]non-3-yl) imidazo[1,5-a]-pyridine-3-carboxamide (E1)



(E1)

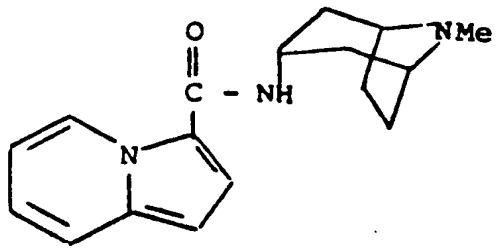
A solution of (endo)-N-(9-methyl-9-azabicyclo[3,3,1] non-3-yl)-N'-(2-pyridylmethyl)oxamide (D.2) (0.3g) in xylene (10ml) was treated with phosphoryl chloride (0.1ml) and then heated under reflux for 18h. The solvent was then removed by evaporation in vacuo and the residue partitioned between CH_2Cl_2 (100ml) and K_2CO_3 solution. The organic extract was dried (K_2CO_3), evaporated and purified by column chromatography on silica to give the title compound (0.1g).

^{1}H-nmr(d^6DMSO)δ	9.45	(d, 1H)
	8.00-7.75	(m, 1H)
	7.63	(d, 1H)
	7.46	(s, 1H)
	7.00	(t, 1H)
	6.85	(t, 1H)
	4.60-4.40	(m, 1H)
	3.20-3.00	(m, 2H)
	2.54	(s, 3H)
	2.45-2.27	(m, 2H)
	2.15-1.90	(m, 3H)
	1.65-1.40	(m, 3H)
	1.05-1.00	(m, 2H)

m.s. M^+ 298.1798; $C_{17}H_{22}N_4O$ requires M^+ 298.1793.

Example 2

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl) indolizin-3-carboxamide (E2)



(E2)

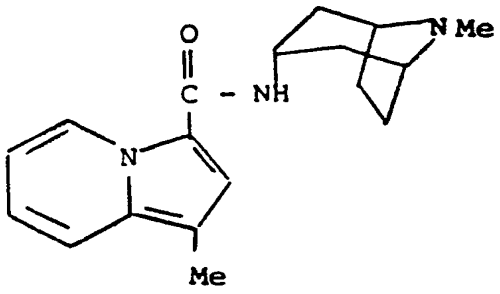
A solution of (endo)-8-methyl-8-azabicyclo[3,2,1] octan-3-amine) (1.0g) and triethylamine (1.0ml) in CH_2Cl_2 (10ml) was added to a stirred solution of indolizin-1-carbonyl chloride (J. Chem. Soc. C. 901 [1969]) (1.4g) in CH_2Cl_2 (100ml). After 1h, the reaction mixture was washed with K_2CO_3 solution, dried (K_2CO_3) and evaporated to dryness. Purification by column chromatography on alumina gave the title compound (0.5g) mp 102-3°

^{1}H-nmr($CDCl_3$)δ	9.56	(d, 1H)
	7.45	(d, 1H)
	7.06	(d, 1H)
	6.92	(t, 1H)
	6.72	(t, 1H)
	6.45	(d, 1H)
	6.25	(brd, 1H)
	4.30	(q, 1H)
	3.23	(brs, 2H)
	2.50-2.10	(m, 7H including 2.34,s,3H)
	2.00-1.70	(m, 4H)

m.s. M^+ 283.1685; $C_{17}H_{21}N_3O$ requires M^+ 283.1685.

Example 3

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-methylindolizin-3-carboxamide (E3)



(E3)

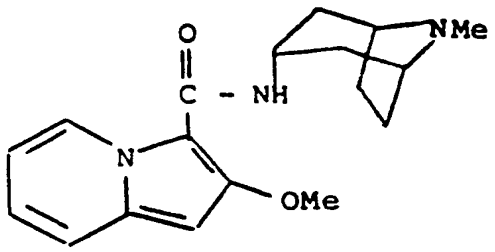
Following the precedures outlined in Example 2; 3-methyl-indolizin-1-carbonyl chloride (0.3g) was converted to the title compound (E.3) (0.16g) mp 169-70°.

^{1}H-nmr($CDCl_3$)δ	9.52	(d, 1H)
	7.38	(d, 1H)
	6.88	(s, t, 2H)
	6.67	(t, 1H)
	6.17	(d, 1H)
	4.28	(q, 1H)
	3.25	(brs, 2H)
	2.40-2.10	(m, 10H including 2.34,s,6H)
	2.00-1.75	(m, 4H)

m.s. M^+ 297.1844; $C_{18}H_{23}N_3O$ requires M^+ 294.1841.

Example 4

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-methoxyindolizin-3-carboxamide (E4)



(E4)

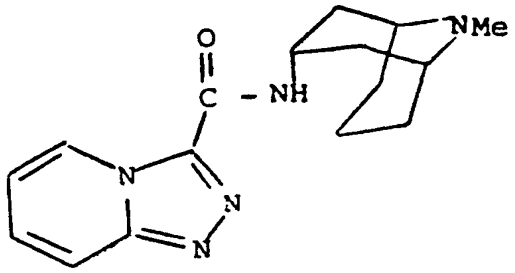
Following the procedures outlined in Example 2; 2-methoxy-indolizin-1-carbonyl chloride (0.3g) was converted to the title compound (0.22g)

^{1}H-nmr($CDCl_3$)δ	9.75	(d, 1H)
	7.68	(d, 1H)
	7.30	(d, 1H)
	6.94	(t, 1H)
	6.68	(t, 1H)
	6.08	(s, 1H)
	4.33	(q, 1H)
	4.04	(s, 3H)
	3.20	(brs, 2H)
	2.40-2.22	(m, 5H including 2.34,s,3H)
	2.20-2.05	(m, 2H)
	2.00-1.85	(m, 2H)
	1.75	(d, 2H)

m.s. M^+ 313.1794; $C_{18}H_{23}N_3O$ requires M^+ 313.1790.

Example 5

(endo)-N-(9-Methyl-9-azabicyclo[3.3.1]non-3-yl)-pyrido[2,1-c]-S-triazole-3-carboxamide (E5)



(E5)

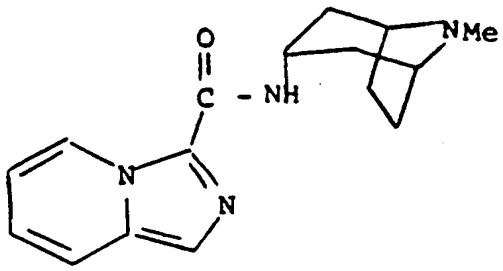
A solution of (endo)-N-(9-methyl-9-azabicyclo[3.3.1]-non-3-yl)-N'-(2-pyridylamino)oxamide (prepared from 2-hydrazino-pyridine as in description 2) (2.0g) was heated under reflux in a Dean and Stark apparatus in xylene (200ml) with tosic acid (0.1g) for 24h. The xylene was removed and the residue partitioned between aqueous $NaHCO_3$ and $CHCl_3$ (200ml). The chloroform extract was dried (K_2CO_3) and evaporated to dryness. Crystallisation of the residue from EtOAc/petrol afforded the title compound (E5) (1.2g) m.p. 193-4°C.

^{1}H-nmr ($CDCl_3$) δ:	9.36	(d, 1H)
	7.86	(d, 1H)
	7.41	(t, 1H)
	7.33	(d, 1H)
	7.02	(t, 1H)
	4.65-4.45	(m, 1H)
	3.14	(brd, 2H)
	2.62-2.44	(m, 5H including 2.52, s, 3H)
	2.10-1.90	(m, 3H)
	1.60-1.35	(m, 3H)
	1.05-1.00	(m, 2H)

Following the procedures outlined in Description 1, 2 and Example 1, the appropriately substituted pyridine and (endo)-8-methyl-8-azabicyclo[3.2.1]octan-3-amine were converted into the following compounds.

Example 6

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)imidazo[1,5-a]pyridine-3-carboxamide monohydrochloride (E6)



.HCl (E6)

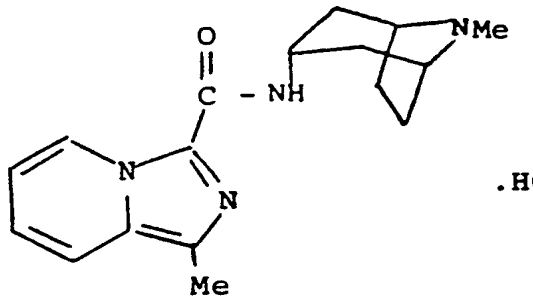
^{1}H-nmr (d^6-DMSO) δ

10.30	(br s, 1H)
9.35	(d, 1H)
8.43	(d, 1H)
7.82	(d, 1H)
7.63	(s, 1H)
7.20-7.00	(m, 2H)
4.10-4.00	(m, 1H)
3.90-3.70	(m, 2H)
2.64	(d, 3H)
2.40-2.10	(m, 7H)

m.s. M^+ 284.1640; $C_{18}H_{20}N_4O$ requires M^+ 284.1649

Example 7

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-methylimidazo[1,5-a]pyridine-3-carboxamide monohydrochloride (E7)



(E7)

.HCl

^{1}H-nmr ($CDCl_3$) δ

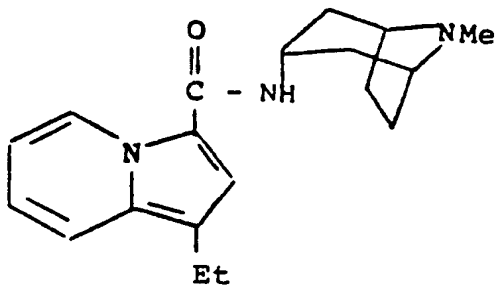
12.35 (br s, 1H)
9.46 (br d, 1H)
7.57 (d, 1H)
7.10-6.80 (m, 2H)
4.37 (q, 1H)
3.80 (br s, 2H)
3.25-3.10 (m, 2H)
2.77 (d, 3H)
2.70-2.10 (m, 10H)

m.s. M^+ 298.1799: $C_{17}H_{22}N_4O_2$ requires M^+ 298.1804

Following the procedure outlined in Example 2: the following compounds were prepared.

Example 8

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-ethyl indolizin-3-carboxamide (E8)



(E8)

m.p. 171-2°C

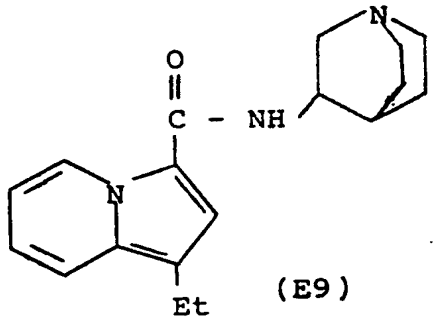
^{1}H-nmr ($CDCl_3$) δ

9.53 (dm, 1H)
7.40 (dm, 1H)
6.92-6.82 (m, 2H including 6.89, s, 1H)
6.67 (tm, 1H)
6.19 (brd, 1H)
4.29 (q, 1H)
3.25 (brs, 2H)
2.76 (q, 2H)
2.40-2.15 (m, 7H including 2.33, s, 3H)
1.95-1.72 (m, 4H)
1.30 (t, 3H)

m.s. M^+ 311.2007; $C_{19}H_{25}N_3O$ requires 311.2017

Example 9

N-(3-Quinuclidinyl)-1-ethylindolizin-3-carboxamide (E9)



(E9)

m.p. 185-6°C

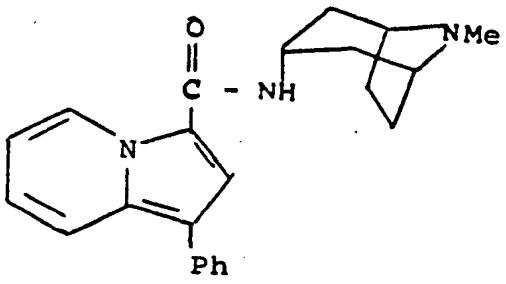
^{1}H-nmr ($CDCl_3$) δ

9.54	(dm, 1H)
7.40	(dm, 1H)
7.05	(s, 1H)
6.89	(tm, 1H)
6.67	(tm, 1H)
6.03	(brd, 1H)
4.26-4.12	(m, 1H)
3.48	(d,d,d, 1H)
3.10-2.65	(m, 7H including 2.78, q, 2H)
2.12-2.05	(m, 1H)
1.92-1.70	(m, 3H)
1.64-1.50	(m, 1H)
1.30	(t, 3H)

m.s. M^+ 297.1852: $C_{18}H_{23}N_3O$ requires 297.1863

Example 10

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-phenylindolizin-3-carboxamide (E10)



(E10)

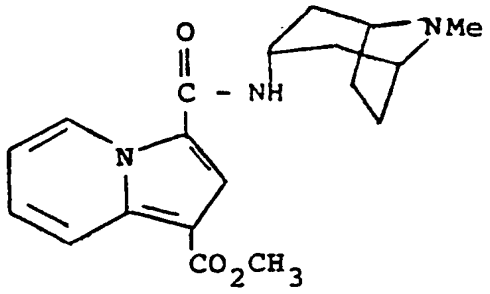
m.p. 148°C

^{1}H-nmr ($CDCl_3$) δ

9.65 (dm, 1H)
7.90-6.60 (m, 9H including 7.18, s, 1H)
6.30 (brd, 1H)
4.32 (q, 1H)
3.20 (brs, 2H)
2.55-1.60 (m, 11H including 2.34, s, 3H)

Example 11

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-methoxycarbonylindolizin-3-carboxamide (E11)



(E11)

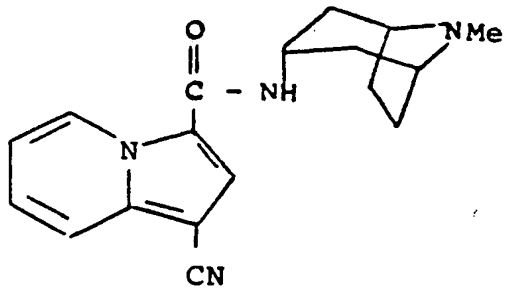
m.p. 183-4°C

^{1}H-nmr ($CDCl_3$) δ

9.68 (dm, 1H)
8.27 (dm, 1H)
7.55 (s, 1H)
7.28 (m, 1H)
6.90 (dt, 1H)
6.31 (brd, 1H)
4.28 (q, 1H)
3.94 (s, 3H)
3.22 (brs, 2H)
2.55-1.55 (m, 11H including 2.34, s, 3H)

Example 12

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-cyanoindolizin-3-carboxamide (E12)



(E12)

m.p. 194-5°C

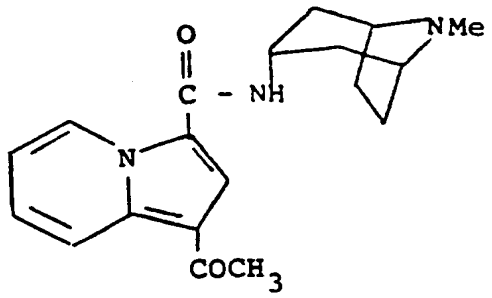
^{1}H-nmr ($CDCl_3$) δ

9.62 (dm, 1H)
7.70 (dm, 1H)
7.33 (s, 1H)
7.33-7.24 (m, 1H)
6.95 (dt, 1H)
6.33 (brd, 1H)
4.28 (q, 1H)
3.26 (brs, 2H)
2.41-2.20 (m, 7H including 2.33, s, 3H)
1.92-1.74 (m, 4H)

m.s. M^+ 308.1637; $C_{18}H_{20}N_4O$ requires 308.1637

Example 13

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-acetylindolizin-3-carboxamide (E13)



(E13)

m.p. 162-3°C

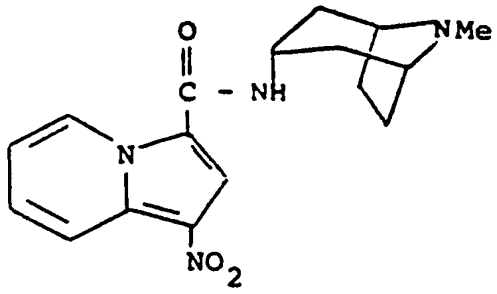
^{1}H-nmr ($CDCl_3$) δ

9.65 (d, 1H)
8.51 (d, 1H)
7.40 (s, 1H)
7.38-7.26 (m, 1H)
6.96 (t, 1H)
6.31 (brd, 1H)
4.31 (q, 1H)
3.25 (brs, 2H)
2.57 (s, 3H)
2.42-2.20 (m, 7H including 2.34, s, 3H)
1.95-1.75 (m, 4H)

m.s. M^+325.1789; $C_{19}H_{23}N_3O_2$ requires 325.1788

Example 14

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-nitro indolizin-3-carboxamide (E14)



(E14)

m.p. 183-5°C

^{1}H-nmr ($CDCl_3$) δ

9.74 (d, 1H)
8.49 (d, 1H)
7.80 (s, 1H)
7.54 (t, 1H)
7.09 (t, 1H)
6.52 (brd, 1H)
4.30 (q, 1H)
3.28 (brs, 2H)
2.50-2.15 (m, 7H including 2.35, s, 3H)
2.00-1.80 (m, 4H)

m.s. M^+ 328.1534; $C_{17}H_{20}N_4O_3$ requires 328.1537

Pharmacology

Antagonism of the von Bezold-Jarisch reflex

The compounds were evaluated for antagonism of the von Bezold-Jarisch reflex evoked by 5-HT in the anaesthetised rat according to the following method:

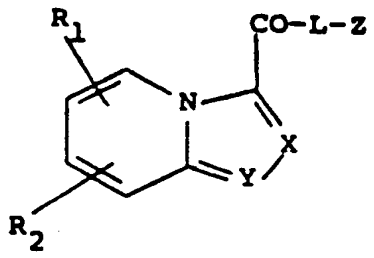
Male rats 250-350g, were anaesthetised with urethane (1.25g/kg intraperitoneally) and blood pressure and heart rate recorded as described by Fozard J.R. et al., J. Cardiovasc. Pharmacol. 2, 229-245 (1980). A submaximal dose of 5-HT (usually 6µg/kg) was given repeatedly by the intravenous route and changes in heart rate quantified. Compounds were given intravenously and the concentration required to reduce the 5-HT-evoked response to 50% of the control response (ED_{50}) was then determined.

The compounds of Examples 1 and 2 had an ED_{50} value of 10mg/µg i.v. and the compound of Example 3 had an ED_{50} value of 1.6 µg/kg/ i.v.

Claims

C

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

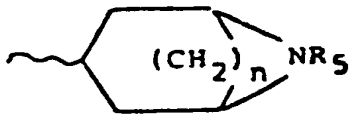
wherein

L is NH or O;

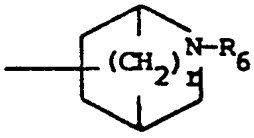
X is N or CR_3 wherein R_3 is hydrogen or C_{1-6} alkoxy;
Y is N or CR_4 wherein R_4 is hydrogen, halogen, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulphonyl, C_{1-6} alkylsulphinyl, C_{1-7} acyl, cyano, C_{1-6} alkoxycarbonyl, C_{1-7} acylamino, hydroxy, nitro or amino, aminocarbonyl, or aminosulphonyl, optionally N-substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, and C_{3-8} cycloalkyl C_{1-4} alkyl or disubstituted by C_4 or C_5 polymethylene; phenyl or phenyl C_{1-4} alkyl group optionally substituted in the phenyl ring by one or two of halogen, C_{1-6} alkoxy or C_{1-6} alkyl groups.

R_1 and R_2 are independently selected from hydrogen, or halogen;

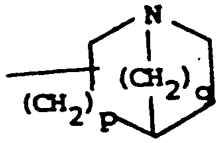
Z is a group of formula (a), (b) or (c):



(a)



(b)

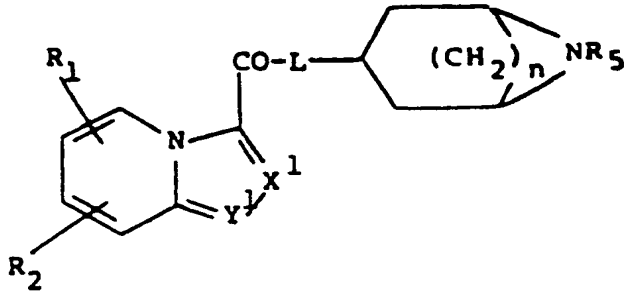


(c)

wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3; and

R_5 or R_6 is C_{1-4} alkyl.

2. A compound according to claim 1 of formula (II):

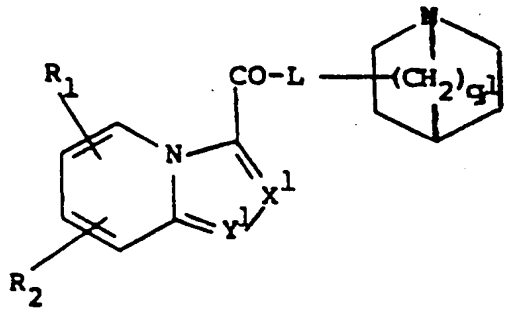


(II)

wherein X^1 is N, H or $COCH_3$, Y^1 is N, H or C-$R_4{}^1$ wherein $R_4{}^1$ is hydrogen, fluoro, chloro, bromo, CF_3, methyl, ethyl, methoxy, ethoxy, methylthio, ethylthio, methylsulphonyl, ethylsulphonyl, methylsulphinyl, ethylsulphinyl, acetyl, propionyl, cyano, methoxycarbonyl, ethoxycarbonyl, acetylamino, hydroxy, nitro; and amino, aminocarbonyl, or aminosulphonyl, any of which may be optionally substituted by one or two methyl groups or by a cyclopentyl or cyclohexyl group or $R_4{}^1$ is phenyl or benzyl optionally substituted by one or two methyl, methoxy, bromo, chloro or fluoro groups; and the remaining variables are as defined in claim 1.

3. A compound according to claim 2 wherein R_5 is methyl.

4. A compound according to claim 1 of formula (III):



(III)

wherein the variable groups are as defined in claims 1 and 2.

5. A compound according to any one of claims 1 to 4 wherein Y is N, CH or CCH_3.

6. A compound according to any one of claims 1 to 5 wherein R_1 and R_2 are both hydrogen.

7. (endo)-N-(9-Methyl-9-azabicyclo[3.3.1]non-3-yl)imidazo[1,5-a]-pyridine-3-carboxamide,

(endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)indolizin-3-carboxamide,

(endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-methylindolizin-3-carboxamide,

(endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-methoxyindolizin-3-carboxamide,

(endo)-N-(9-methyl-9-azabicyclo[3.2.1]non-3-yl)pyrido[2,1-c]-S-triazole-3-carboxamide,

(endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)imidazo[1,5-a]-pyridine-3-carboxamide,

(endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-methylimidazo[1,5-a]pyridine-3-carboxamide,

(endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-ethylindolizin-3-carboxamide,

N-(3-quinuclidinyl)-1-ethylindolizin-3-carboxamide,

(endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-phenylindolizin-3-carboxamide,

(endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-methoxycarbonylindolizin-3-carboxamide,

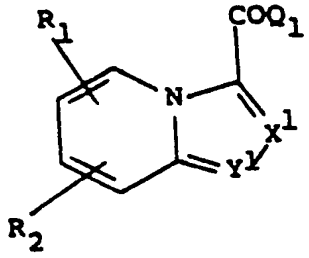
(endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-cyanoindolizin-3-carboxamide,

(endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-acetylindolizin-3-carboxamide,

(endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-nitroindolizin-3-carboxamide,

or a pharmaceutically acceptable salt of any of the foregoing.

8. A process for the preparation of a compound according to claim 1, which process comprises reacting a compound of formula (V):



(V)

with a compound of formula (VI):

$$H - L - Z^1 \qquad (VI)$$

or a reactive derivative thereof, when L is O;

wherein Q_1 is a leaving group; Z^1 is Z as defined in claim 1 or wherein R_5/R_6 is replaced by a hydrogenolysable protecting group; and the remaining variables are as defined in claim 1; and thereafter optionally converting any R_1 and/or R_2 group to another R_1/R_2 group respectively, converting Z^1,

when other than Z, to Z; and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

9, A pharmaceutical composition comprising a compound according to any one of claims 1 to 7, and a pharmaceutically acceptable carrier.

10. A compound according to claim 1 for use in the treatment of migraine, cluster headache, trigeminal neuralgia and/or emesis, in mammals.

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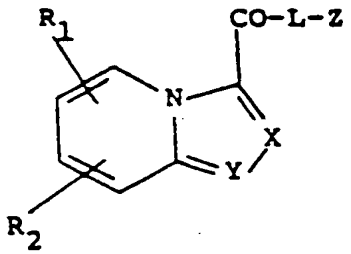
(54) **Azabicyclic compounds, process for their preparation, and their pharmaceutical use.**

(57) Compounds of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

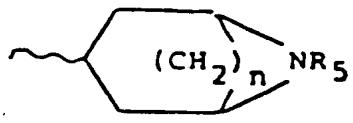
L is NH or O;

X is N or CR_3 wherein R_3 is hydrogen or C_{1-6} alkoxy;

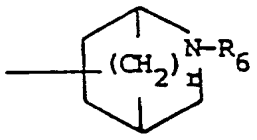
Y is N or CR_4 wherein R_4 is hydrogen, halogen, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulphonyl, C_{1-6} alkylsulphinyl, C_{1-7} acyl, cyano, C_{1-6} alkoxycarbonyl, C_{1-7} acylamino, hydroxy, nitro or amino, aminocarbonyl, or aminosulphonyl, optionally N-substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, and C_{3-8} cycloalkyl C_{1-4} alkyl or disubstituted by C_4 or C_5 polymethylene; phenyl or phenyl C_{1-4} alkyl group optionally substituted in the phenyl ring by one or two of halogen, C_{1-6} alkoxy or C_{1-6} alkyl groups.

R_1 and R_2 are independently selected from hydrogen, or halogen;

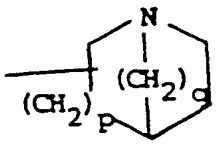
Z is a group of formula (a), (b) or (c):



(a)



(b)



(c)

wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3; and

R_5 or R_6 is C_{1-4} alkyl; having 5-HT_3 antagonist activity, a process for their preparation and their use as pharmaceuticals.

Croydon Printing Company Ltd.

European Patent Office

EUROPEAN SEARCH REPORT

0254584

Application Number

EP 87 30 6548

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	WO-A-8 501 048 (SANDOZ) * claims 2,3,12 *	1,10	C 07 D 451/04 C 07 D 451/14 C 07 D 453/02 A 61 K 31/46 A 61 K 31/435
A,P	EP-A-0 200 444 (BEECHAM GROUP) * claims 1, 12, 15, 17 *	1,8,9, 10	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K 31/435
A 61 K 31/46
C 07 D 451/04
C 07 D 451/14
C 07 D 453/02
C 07 D 519/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	03-02-1989	KNAACK

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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E : earlier patent document, but published on, or after the filing date
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